(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 333 349 B1**

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **13.04.94**

(51) Int. Cl.5: **A61K 31/135**, A61K 31/44, A61K 37/36, A61K 37/43, A23K 1/16

(21) Application number: **89302096.6**

(22) Date of filing: **02.03.89**

(54) Phenethanolamine and growth hormone combinations.

(30) Priority: **07.03.88 US 164675**

(43) Date of publication of application:
20.09.89 Bulletin 89/38

(45) Publication of the grant of the patent:
13.04.94 Bulletin 94/15

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 0 272 976
US-A- 4 690 951
US-A- 4 792 546

ANIMAL PRODUCTION, vol. 44, 1987, GB; P.E.V. WILLIAMS et al., p. 475&NUM;

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Description

This invention provides a combination product useful for improving feed efficiency, growth rate, and carcass quality of pigs. It also provides related growth promotion methods.

Ractopamine and its use as a growth promoter for pigs are disclosed in U.S. 4,690,951.

Growth hormone and growth hormone related substances are also recognized growth promoters for pigs. J. Anim. Sci. 35 (4), 794-800 (1972). However, certain disadvantages accompany use of exogenously administered growth hormone and growth hormone related substances. More specifically, the ratio of carcass weight to live weight (dressing percent) is reduced when growth hormone is used. This arises because growth hormone increases rate of viscera growth faster than it increases rate of carcass (muscle, bone, skin, and fat) growth. Further, use of growth hormone causes increased blood sugar and insulin levels which can be detrimental to the health of the pigs.

Compositions containing phenethanolamines and BGH, affecting the growth of calves, are described in Animal Production 44 (54) 1987, 475. EP-A-6735 describes the antihyperglycaemic activity of some phenethanolamines.

The present invention provides a composition comprising an exogenous growth hormone related substance suitable for administration to swine in combination with ractopamine.

The invention also provides a method of improving growth, feed efficiency, or carcass quality of a pig which comprises administering both a growth hormone related substance and ractopamine, to the pig.

The invention also provides a method of reducing a greater than normal blood sugar level or improving growth promotion or feed efficiency or carcass quality in a pig that has received a dose of growth hormone related substance, which comprises administering ractopamine.

Ractopamine is the generic name for 4-hydroxy-α-[[[3-(4-hydroxyphenyl)-1-methylpropyl]amino]methyl]-benzenemethanol. Preparation of this compound, its salts and congeners, and their use as growth promoters are disclosed in U.S. 4,690,951. The term "ractopamine" as used herein refers not only to the free base, but also to acid addition salts thereof. Ractopamine can be administered by either an oral or parenteral route.

The term "growth hormone related substance" includes growth hormone (somatotropin), growth hormone releasing factor, somatomedin, or any substance that stimulates the production of endogenous growth hormone and the production of somatomedin. Substances that stimulate endogenous growth hormone include enkephalins or enkephalin-like compounds, prostaglandins, alpha-adrenergics, benzodiazapines, barbiturates, opiate antagonists, gamma-aminobutyric acid (GABA), GABAergic compounds, and the like. Other substances that can be administered include any analogues of growth hormone or growth hormone releasing factor such as methionyl bovine growth hormone, 29 amino acid growth hormone releasing factor, and the like. Administration of growth hormone can also be achieved by implanting cells which produce growth hormone for example, pituitary tumor cells, or cells which produce growth hormone releasing factor.

The growth hormone related substance can be a natural or recombinant product, or it can be prepared by solid-phase synthetic procedures. In addition, the growth hormone or related substance need not be species specific. For example, porcine, bovine, or human growth hormone can be used in the administration of growth hormone to pigs.

Due to the protein nature of the growth hormone related substance, it is not desirable to administer it in an oral form. Intramuscular, intravenous, or subcutaneous injections can be used; also the growth hormone related substance can be delivered from an implant.

In accordance with the growth promotion methods provided by the invention, the ractopamine, and the growth hormone related substance may be administered either separately or in combined form. When administered separately, the growth hormone related substance will typically be administered parenterally, and the ractopamine, will be delivered orally, e.g. in the animal's feed, but can also be delivered parenterally.

The compositions of the invention, which contain both the growth hormone related substance and ractopamine, will typically be combined with a carrier to enable parenteral delivery of the combination. A suitable carrier for parenteral injection, for example, is .2 M potassium phosphate buffer.

In addition, the composition may be administered by implant, or by other drug delivery devices, such as microcapsules, pumps, and the like.

The amounts of the substances to be employed in the present invention will vary and are not critical so long as the amounts are effective. In general, the present invention contemplates that 0.05 to 100 mg/head/day of ractopamine, and 0.5 to 10 mg/head/day of growth hormone related substance will be delivered to swine. Preferably, the amount of ractopamine delivered is in the range of 0.25 to 60

mg/head/day. The preferred amount of growth hormone related substance is 1.5 to 6.0 mg/head/day. Preferred compositions of the invention contain ractopamine and pGH in a weight ratio of from 0.25/3 to 60/1.5.

It will be understood that daily administration is not necessary, and that the recommended amounts are averages. Thus, biweekly injections may be used, for example. If implants are used, administration may be semiweekly, or at even greater intervals. If administered in the feed, an appropriate amount of ractopamine is 1 to 30 ppm, preferably 2.5 to 20 ppm.

The amount of protein in the diet of treated animals is an important consideration. Typical feed rations for finishing pigs (i.e., those weighing from about 75 lbs to market weight) contain 13% to 16% protein. If swine weighing 34 kg (75 lbs) and up receive porcine growth hormone and a diet that contains only 13% to 16% protein, however, then little additional improvement in growth rate is observed if ractopamine is also administered. In accordance with one aspect of this invention, the diet protein level should be greater than 16%, preferably above 18%, and more preferably 20% or above. These higher protein levels can also be achieved by supplementing lower protein diets with the limiting amino acids to make them equivalent to higher protein level diets. Then the additional administration of ractopamine to an animal receiving porcine growth hormone does provide an additive increase in growth rate.

As demonstrated in the following experimental results, simultaneous treatment with both growth hormone and ractopamine improves carcass parameters, including dressing percent, percent fat-free muscle, loin eye area, and leanness. These advantages are obtained even with the diet containing the lower levels of crude protein.

Experimental results also show that combined treatment reduces blood glucose and insulin levels compared to those observed when pigs are treated with pGH alone.

EXPERIMENT 1

This experiment evaluated the effect of separate or combined treatment of finishing swine with pGH and ractopamine. In this case the diet contained a calculated 16.68% crude protein. Barrows and gilts, weighing an average of about 136 lbs, were allocated to four treatment groups. The first group was the control group. The second group of animals received daily subcutaneous injections of pGH (in sterilized .2 M potassium phosphate buffer); for the first 28 days, each animal received 3 mg/day, and thereafter until the end of the trial, each animal received 4 mg/day. A third group of animals received ractopamine at a rate of 10 ppm in their feed. The fourth group received both daily subcutaneous injections of pGH and ractopamine in their feed at 10 ppm; the pGH was supplied in the amount of 3 mg/day for the first 28 days and in the amount of 4 mg/day thereafter until the end of the trial. The first and third groups also received daily injections of .2 M potassium phosphate buffer solution.

The feed ration used was the following:

INGREDIENT	PERCENT
Corn, Yellow, Ground	76.70
Soybean Oil Meal, Solvent Extracted, Dehulled, 50%	19.35
Calcium Carbonate	1.20
Dicalcium Phosphate, Feed Grade	1.20
Salt (NaCl)	0.50
Other Ingredients (minerals + vitamins + methionine)	1.05
Total	100.00

The animals continued on treatment for an average of 52 days. The following table gives a summary of the observed results. The column headed "Feed/Gain" reports the "Average Daily Feed" divided by the "Average Daily Gain". The table shows that when a feed ration containing only 16.7% crude protein is used, the "Feed/Gain" ratio is not improved by combining ractopamine and pGH treatment. The column headed "Dressing %" reports the ratio of the average hot carcass weight to the average final live weight. It shows that by combining ractopamine and pGH treatment the reduction in dressing % observed with pGH treatment is reversed.

Treatment Description	No. Pigs	Avg Days on Test	Total Animal Days	Avg Initial Weight (Kg)	Avg Final Weight (Kg)	Avg Gain (Kg)	Avg Daily Gain (Kg)	Total Feed (Kg)	Avg Daily Feed (Kg)	Feed Gain	Dressing (%)	10th Rib Fat (cm)	10th Rib Loin Eye Area (sq cm)	Est Fat-Free Muscle (%)
Control	15	54.5	817	60.3	103.7	43.2	0.79	2367	2.87	3.65	74.3	2.57	30.77	49.3
pGH	14	53.0	742	61.7	104.4	42.8	0.81	1911	2.57	3.18	73.0	2.31	33.23	51.1
Ractopamine	14	47.0	658	61.2	104.9	43.4	0.91	1876	2.81	3.09	74.3	2.44	34.97	51.4
pGH + Ractopamine	15	49.8	747	61.2	104.8	43.4	0.86	2018	2.69	3.12	74.0	2.21	36.65	52.9

EXPERIMENT 2

This experiment evaluated the effect of separate or combined treatment of finishing swine with pGH and ractopamine, with the diet containing 20% crude protein. Barrows, each weighing about 68 kg (149 lbs),

were randomly allocated to four treatment groups. The first group was the control group. A second group of animals received daily 4 ml injections (i.m.) containing pGH (in .2 M potassium phosphate buffer) at a rate of approximately 60 µg/kg of body weight, which amounted to between 4 and 8 mg/head/day (dose adjusted every two weeks). A third group of animals received ractopamine at a rate of 10 ppm in their feed. The fourth group received daily 4 ml injections containing pGH at the rate of approximately 60 µg/kg of body weight and ractopamine in their feed at 10 ppm. The first and third groups also received daily injections of 4 ml of .2 M potassium phosphate buffer solution.

The feed ration used was the following:

INGREDIENT	PERCENT
Corn, Yellow, Ground (8% C.P.)	58.31
Soybean Oil Meal (48% C.P.)	32.00
Dicalcium Phosphate	2.25
Calcium Carbonate	1.00
Salt	0.62
Other Ingredients (minerals + vitamins)	0.82
Animal Fat	5.00
	100.00

The animals continued treatment for an average of 60 days. The following table gives a summary of the observed results. Animals receiving combined treatment with pGH and ractopamine showed the highest daily gains, the best feed efficiency (lowest Feed/Gain), least fat, largest loin eye area, greatest percent fat-free muscle, and a dressing percent identical to controls.

Treatment Description	No. Pigs	Avg Days on Test	Total Animal Days	Avg Initial Weight (Kg)	Avg Final Weight (Kg)	Avg Gain (Kg)	Avg Daily Gain (Kg)	Total Feed (Kg)	Avg Daily Feed (Kg)	Feed Gain	Dressing (%)	10th Rib Fat (cm)	10th Rib Loin Eye Area (sq cm)	Est Fat-Free Muscle (%)
Control	12	64.4	773	67.6	124.0	56.6	0.88	2403	3.11	3.56	74.1	3.58	34.32	47.5
pGH	12	58.7	704	67.6	126.7	59.1	1.01	2005	2.85	2.84	73.0	2.95	41.48	52.6
Ractopamine	10	59.6	596	67.6	124.8	57.2	0.94	1585	2.65	2.80	75.0	2.77	46.19	55.2
pGH + Ractopamine	11	55.7	613	67.1	123.7	56.4	1.02	1677	2.71	2.66	74.1	2.39	47.23	56.8

EXPERIMENT 3

Nitrogen retention is a good indicator for feed efficiency. This experiment evaluated the effect on nitrogen retention of separate versus combined treatment with porcine growth hormone (pGH) and

ractopamine (EL-737) when the diet contained 16% or 20% crude protein.

Twenty-four crossbred barrows, each weighing approximately 60 kg were acclimated to individual metabolism cages. For a period of one week, half of the animals received a diet containing 16.3% crude protein, and the other animals received a diet containing 20% crude protein. Then, three animals that were receiving the diet with 16.3% crude protein were allocated to each of four treatments: (1) control animals that continued to receive a diet containing 16.3% crude protein, (2) animals that continued to receive a diet containing 16.3% crude protein and also received daily subcutaneous injections of 3 mg of pGH (in 3 ml of sterilized .2 M potassium phosphate buffer, pH 7.8), (3) animals that continued to receive a diet containing 16.3% crude protein and also received ractopamine at the rate of 20 ppm in their feed, (4) animals that continued to receive a diet containing 16.3% crude protein and also received both daily injections of 3 mg of pGH and 20 ppm of ractopamine in their feed; and three animals that were receiving the diet with 20% crude protein were allocated to each of four treatments, corresponding to the first four: (5) control animals that continued to receive a diet containing 20% crude protein, (6) animals that continued to receive a diet containing 20% crude protein and also received daily subcutaneous injections of 3 mg of pGH, (7) animals that continued to receive a diet containing 20% crude protein and also received ractopamine at the rate of 20 ppm in their feed, and (8) animals that continued to receive a diet containing 20% crude protein and also received both daily injections of 3 mg of pGH and ractopamine at the rate of 20 ppm in their feed. Animals in groups 1, 3, 5, and 6 also received daily subcutaneous injections of .2 M potassium phosphate buffer.

The two feed rations used had the following compositions:

16.3% Crude Protein Ration	
Corn, Yellow, Ground (8% C.P.)	74.75%
Soybean Oil Meal (48% C.P.)	21.50
Dicalcium Phosphate	1.80
Calcium Carbonate	0.80
Salt	0.50
Other Ingredients (minerals + vitamins)	0.65
	100.00%

20% Crude Protein Ration	
Corn, Yellow, Ground (8% C.P.)	65.50%
Soybean Oil Meal (48% C.P.)	30.75
Dicalcium Phosphate	1.80
Calcium Carbonate	0.80
Salt	0.50
Other Ingredients (minerals + vitamins)	0.65
	100.00%

The animals received treatment for nine days. Then treatment was discontinued, and thereafter the animals that had been fed the diet containing 16.3% crude protein, instead received the diet containing 20%. Similarly, the animals that had been fed the diet containing 20% crude protein, instead received the diet containing 16.3%. After a nine day adaptation period, treatment resumed, with each animal receiving the same treatment it had previously, except for the level of dietary protein, which was the opposite level from that which it received in the first treatment period. Treatment continued for nine days. Accordingly, a total of six animals received each of the eight treatments.

During the experiment, urine was collected, and the amount of nitrogen excreted in the urine was determined for each animal. The results of this experiment are reported in the following table, which shows that combined treatment of finishing swine with pGH and ractopamine substantially reduced nitrogen excretion as compared to controls and separate treatment with one compound or the other, when the level of crude protein was 20%.

	Urinary Urea, g/day			
	No. Pigs	16% Protein	No. Pigs	20% Protein
Control	6	21.0	6	28.7
pGH (3 mg/day)[1]	6	16.8	6	22.6
EL-737 (20 ppm)	6	16.3	6	21.6
EL-737 + pGH[1]	6	16.0	6	18.2

[1] 3 mg in KH_2PO_4 carrier was injected S.Q. daily.

EXPERIMENT 4

Twenty crossbred barrows, each weighing approximately 79 kg (175 pounds), maintained in individual metabolism cages, with an indwelling cannula surgically inserted into the femoral vein, were used to determine the effect of ractopamine on reducing the hyperglycemic and hyperinsulinemic activity of growth hormone. Five barrows were assigned to each of four groups, using a randomized block design, blocking on pretreatment insulin levels. One group was the control group. A second group received pGH (6 mg/day SQ). A third received ractopamine (20 ppm in feed). The fourth group received the combination of pGH (6 mg/day SQ) and ractopamine (20 ppm in feed). The pigs were accustomed to a feeding regime of 2000 g of feed per day, equally divided between two feedings. This was approximately 70-80% of ad libitum intake. The diet contained 16% crude protein. Blood samples were taken on the day prior to initiation of treatment (-1), on the first day of treatment (day 0), day 3, day 7, and day 14 of treatment. Samples were taken at -0.5, +0.25, +0.5, +1.0, +1.5, +2.0, +3.0, and +6.0 hours relative to the treatment injection and/or the a.m. feeding on each of the above days. Samples were assayed for glucose and insulin.

The averages of the samples taken on days 3 and 7 are shown in the following table. The data taken on day 0, which are omitted from the table, showed the expected short term increase in glucose and insulin levels that is characteristic on administration of phenethanolamines. The data taken on day 14 are omitted from the summary, because two pigs with particularly high glucose and insulin levels in the pGH treatment group quit eating. Since they were not eating, treatment was stopped and no blood samples were taken from these pigs on day 14. The data would have been skewed by the absence of these pigs' data. The remaining chronic treatment data (days 3 and 7) demonstrates that pGH, alone, significantly increased serum insulin and serum glucose levels. Ractopamine, given in combination with pGH, produced a long term reduction in the hyperglycemic/hyperinsulinemic effect of pGH by itself.

	Glucose (mg/dl)	
	Day -1	Days 3 and 7
Control	96.5	93.8
pGH	100.3	105.8
EL-737	96.4	93.7
EL-737 + pGH	96.7 NS	98.7*

NS Value not significantly different from value obtained with pGH administration alone

* Value is significantly different ($P < .06$) from value obtained with pGH administration alone

	Insulin (microunits/ml)	
	Day -1	Days 3 and 7
Control	28.1	28.8
pGH	38.8	53.9
EL-737	27.0	19.6
EL-737 + pGH	32.1 NS	30.2*

NS Value not significantly different from value obtained with pGH administration alone

* Value is significantly different ($P < .06$) from value obtained with pGH administration alone

Claims

1. A composition comprising
   (a) ractopamine, as a first component; and
   (b) an exogenous growth hormone related substance suitable for administration to swine as a second component.

2. The composition of claim 1 wherein the second component is porcine growth hormone or a growth hormone releasing factor.

3. A method for improving growth promotion, of feed efficiency, or carcass quality of pigs receiving a diet containing 20% or more crude protein which comprises administering to the pigs
   ractopamine, and
   a second substance which is a growth hormone related substance.

4. Use of ractopamine for the manufacture of a medicament for reducing a greater than normal insulin or blood sugar level in a pig that has received a dose of a growth hormone related substance.

5. A method of increasing the lower than normal expected dressing percent of a pig that has received a dose of a growth hormone related substance, which comprises administering ractopamine to the pig.

6. A method for preparing a composition for improving growth promotion, feed efficiency, or carcass quality of pigs, which comprises admixing
   (a) ractopamine, with
   (b) an exogenous growth hormone related substance suitable for administration to swine, and
   (c) a carrier to enable parenteral delivery of the composition.

Patentansprüche

1. Zusammensetzung, umfassend (a) Ractopamin als erste Komponente und (b) eine exogene, mit dem Wachstumshormon verwandte Substanz, die geeignet ist zur Verabreichung an Schweine, als zweite Komponente.

2. Zusammensetzung nach Anspruch 1, worin die zweite Komponente Schweinewachstumshormon oder Wachstumshormonfreisetzungfaktor ist.

3. Verfahren zur Verbesserung der Wachstumsförderung oder der Futtereffizienz oder der Fleischqualität von Schweinen, die eine Nahrung mit 20% oder mehr Rohprotein erhalten, umfassend, daß man den Schweinen Ractopamin und eine zweite Substanz, die eine mit dem Wachstumshormon verwandte Substanz ist, verabreicht.

4. Verwendung von Ractopamin für die Herstellung eines Arzneimittels zur Verminderung eines höheren Insulin- oder Blutzuckerpegels als normal bei einem Schwein, das eine Dosis einer mit dem Wachstumshormon verwandte Substanz erhalten hat.

5. Verfahren zur Erhöhung eines geringeren Aufarbeitungsprozentanteils als erwartet bei einem Schwein, das eine Dosis einer mit dem Wachstumshormon verwandten Substanz erhalten hat, das umfaßt, daß man dem Schwein Ractopamin verabreicht.

6. Verfahren zur Herstellung einer Zusammensetzung zur Verbesserung der Wachstumsförderung, der Nahrungseffizienz oder der Fleischqualität von Schweinen, umfassend, daß man (a) Ractopamin mit (b) einer exogenen, mit dem Wachstumshormon verwandten Substanz, die geeignet ist zur Verabreichung an Schweine, und (c) einem Träger, der eine parenterale Zuführung der Zusammensetzung ermöglicht, vermischt.

Revendications

1. Composition comprenant
   (a) de la ractopamine à titre de premier composant, et
   (b) une substance apparentée à une hormone de croissance exogène et appropriée pour l'administration à des porcs, à titre de second composant.

2. Composition selon la revendication 1, dans laquelle le second composant est l'hormone de croissance porcine ou un facteur libérant l'hormone de croissance.

3. Procédé pour améliorer la stimulation de la croissance ou le rendement de la nourriture ou encore la qualité bouchère de porcs recevant un régime alimentaire contenant 20% ou plus de protéines brutes, qui comprend le fait d'administrer aux porcs
   de la ractopamine, et
   une seconde substance, à savoir une substance apparentée à l'hormone de croissance.

4. Utilisation de la ractopamine pour la préparation d'un médicament destiné à réduire un taux de glycémie ou un taux d'insuline supérieur à la normale chez un porc qui a reçu une dose d'une substance apparentée à l'hormone de croissance.

5. Procède pour augmenter le pourcentage escompté inférieur à la normale de rendement à l'abattage d'un porc qui a reçu une dose d'une substance apparentée à l'hormone de croissance, qui comprend le fait d'administrer de la ractopamine au porc.

6. Procédé pour préparer une composition pour améliorer la stimulation de la croissance, le rendement de la nourriture ou la qualité bouchère de porcs, qui comprend le fait de mélanger
   (a) de la ractopamine avec
   (b) une substance apparentée à une hormone de croissance exogène, appropriée pour être administrée à des porcs, et
   (c) un support pour permettre l'administration de la composition par voie parentérale.